PET-guided eBEACOPP treatment of advanced-stage Hodgkin lymphoma (HD18): follow-up analysis of an international, open-label, randomised, phase 3 trial

Stefanie Kreissl, Helen Goergen, Ina Buehnen, Carsten Kobe, Alden Moccia, Richard Greil, Dennis A Eichenauer, Josée M Zijlstra, Jana Markova, Julia Meissner, Michaela Feuring-Buske, Martin Soekler, Hans-Joachim Beck, Wolfgang Willenbacher, Wolf-Dieter Ludwig, Thomas Pabst, Max S Topp, Felicitas Hitz, Martin Bentz, Ulrich Bernd Keller, Dagmar Kühnhardt, Helmut Ostermann, Bernd Hertenstein, Walter Aulitzky, Georg Maschmeyer, Tom Vieler, Hans Eich, Christian Baues, Harald Stein, Michael Fuchs, Volker Diehl, Markus Dietlein, Andreas Engert, Peter Borchmann on behalf of the German Hodgkin Study Group

Lancet Haematol 2021
8: e398–409

See **Comment** page e384

For the German translation of the abstract see **Online** for appendix 1

German Hodgkin Study Group, Department I of Internal Medicine and Center of Integrated Oncology Aachen, Bonn, Cologne, Düsseldorf, German Hodgkin Study Group, Faculty of Medicine and University Hospital of Cologne, University of Cologne, Cologne, Germany (S Kreissl MD, H Goergen Dipl-Math, I Buehnen MA, D A Eichenauer MD, M Fuchs MD, Prof V Diehl MD, Prof A Engert MD, Prof P Borchmann MD); **Department of Nuclear Medicine, University Hospital of Cologne, University of Cologne, Cologne, Germany** (Prof C Kobe MD, Prof M Dietlein MD); **Department of Medical Oncology, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland** (A Moccia MD); **Swiss Group for Clinical Cancer Research (SAKK), Bern, Switzerland** (A Moccia, Prof T Pabst MD, F Hitz MD); **IIIrd Medical Department, Paracelsus Medical University and Salzburg Cancer Research Institute, Salzburg, Austria** (Prof R Greil MD); **Salzburg Cancer Research Institute and Arbeitsgemeinschaft Medikamentöse Tumortherapie, Salzburg, Austria** (Prof R Greil, W Willenbacher MD); **VU University Medical Center, Amsterdam, Netherlands** (J M Zijlstra MD); **Department of Internal Medicine – Hematology, University Hospital Kralovske Vinohrady,**

Summary

Background The German Hodgkin Study Group's HD18 trial established the safety and efficacy of PET-guided eBEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone in escalated doses) for the treatment of advanced-stage Hodgkin lymphoma. However, because of a protocol amendment during the enrolment period (June 1, 2011) that changed standard treatment from eight to six cycles, the results of the HD18 trial have been partially immature. We report a prespecified 5-year follow-up analysis of the completed HD18 trial.

Methods HD18 was an international, open-label, randomised, phase 3 trial done in 301 hospitals and private practices in five European countries. Patients aged 18–60 years with newly diagnosed, advanced-stage Hodgkin lymphoma and an Eastern Cooperative Oncology Group performance status of 0–2 were recruited. After receiving an initial two cycles of eBEACOPP (1250 mg/m² intravenous cyclophosphamide [day 1], 35 mg/m² intravenous doxorubicin [day 1], 200 mg/m² intravenous etoposide [day 1–3], 100 mg/m² oral procarbazine [day 1–7], 40 mg/m² oral prednisone [day 1–14], 1·4 mg/m² intravenous vincristine [day 8], and 10 mg/m² intravenous bleomycin [day 8]), patients underwent a contrast-enhanced CT and PET scan (PET-2). Patients with positive PET-2 were randomly assigned to receive standard therapy (an additional six cycles of eBEACOPP; ie, eight cycles in total) or experimental therapy (an additional six cycles of eBEACOPP plus 375 mg/m² intravenous rituximab; ie, eight cycles in total) until June 1, 2011. After June 1, 2011, all patients with positive PET-2 were assigned to the updated standard therapy with an additional four cycles of eBEACOPP (ie, six cycles in total). Patients with negative PET-2 were randomly assigned (1:1) to receive standard therapy (an additional six cycles of eBEACOPP [ie, eight cycles in total] until June 1, 2011; an additional four cycles of eBEACOPP [ie, six cycles in total] after June 1, 2011) or experimental therapy (an additional two cycles of eBEACOPP; ie, four cycles in total). Randomisation was done centrally with the minimisation method, including a random component, stratified by centre, age, stage, international prognostic score, and sex. The primary endpoint was progression-free survival. HD18 aimed to improve 5-year progression-free survival by 15% in the PET-2-positive intention-to-treat cohort and to exclude inferiority of 6% or more in 5-year progression-free survival in the PET-2-negative per-protocol population. This study is registered with ClinicalTrials.gov, NCT00515554, and is completed.

Findings Between May 14, 2008, and July 18, 2014, 2101 patients were enrolled and 1945 were assigned to a treatment group according to their PET-2 result. In the PET-2-positive cohort, with a median follow-up of 73 months (IQR 59 to 94), 5-year progression-free survival was 89·9% (95% CI 85·7 to 94·1) in 217 patients assigned to eight cycles of eBEACOPP before the protocol amendment and 87·7% (83·1 to 92·4) in 217 patients assigned to eight cycles of rituximab plus eBEACOPP (p=0·40). Among 506 patients who received six cycles of eBEACOPP after the protocol amendment, 5-year progression-free survival was 90·1% (95% CI 87·2 to 92·9), with a median follow-up of 58 months (IQR 39 to 66). In the PET-2-negative cohort, with a median follow-up of 66 months (IQR 54 to 85) in the combined pre-amendment and post-amendment groups, 5-year progression-free survival was 91·2% (95% CI 88·4 to 93·9) in 446 patients who received eight or six cycles of eBEACOPP and 93·0% (90·6 to 95·4) in 474 patients who received four cycles of eBEACOPP (difference 1·9% [95% CI –1·8 to 5·5]). In the subgroup of PET-2-negative patients randomly assigned after protocol amendment, 5-year progression-free survival was 90·9% (95% CI 86·8 to 95·1) in 202 patients assigned to receive six cycles of eBEACOPP and 91·0% (86·6 to 95·5) in 200 patients assigned to receive four cycles of eBEACOPP (difference 0·1% [–5·9 to 6·2]).

Interpretation Long-term follow-up confirms the efficacy and safety of PET-2-guided eBEACOPP in patients with advanced-stage Hodgkin lymphoma. The reduction from eight to four cycles of eBEACOPP represents a benchmark in the treatment of early-responding patients, who can now be potentially cured with a short and safe treatment approach.

Funding Deutsche Krebshilfe, Swiss State Secretariat for Education, Research and Innovation SERI (Switzerland), and Roche Pharma.

Introduction

Patients with newly diagnosed advanced-stage Hodgkin lymphoma face an excellent long-term prognosis, reaching overall survival rates of 95% and higher when treated with the eBEACOPP regimen.[1,2] However, the aim of potentially curing all patients with intensive first-line treatment implies a high burden of treatment for all patients. As both acute and long-term sequelae can severely affect patients' lives,[3–7] we aimed to reduce the overall treatment burden by introducing a response-adapted and thus individualised treatment approach. In general, the concept of response-adapted therapy in advanced-stage Hodgkin lymphoma has yielded two different therapeutic strategies based on the initial treatment intensity. Low-intensity first-line therapy (eg, the ABVD [doxorubicin, bleomycin, vinblastine, and dacarbazine] regimen) primarily requires intensifying treatment for poor metabolic responders to improve lymphoma control. By contrast, high-intensity first-line therapy such as eBEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone in escalated doses) is being reduced in good responders, with the aim of improving safety. In the HD18 study, we used ^{18}F-fluoro-2-deoxy-D-glucose (FDG) PET for metabolic response assessment[8–10] after two cycles of eBEACOPP (PET-2)[11] to guide further treatment. In the PET-2-positive cohort, addition of rituximab did not improve the efficacy of eBEACOPP. In the PET-2-negative cohort, the HD18 trial showed that a reduction from initially eight to four chemotherapy cycles was possible without a clinically relevant loss of efficacy, whereas treatment-related morbidity and mortality were markedly reduced.

However, the analysis of patients with a negative PET-2 result was affected by a protocol amendment on June 1, 2011, in which standard treatment was reduced from eight to six cycles of eBEACOPP, on the basis of the results of the German Hodgkin Study Group's HD15 trial.[1] In the primary analysis of the HD18 trial, the pre-amendment control group receiving eight cycles of eBEACOPP and the post-amendment control group receiving six cycles of eBEACOPP were pooled and compared with the group of patients assigned to four cycles of eBEACOPP. The corresponding subgroup analysis of patients who were randomly assigned after standard treatment had been changed from eight to six cycles had limited power, with a median follow-up of only 39 months (IQR 28–51). It was, thus, unclear whether the reduction to four cycles would also prove beneficial compared with the newer standard of six cycles.

Research in context

Evidence before this study

The primary analysis of the German Hodgkin Study Group's HD18 trial showed that a reduction from initially eight or six cycles of eBEACOPP to four cycles was possible for patients with a negative PET-2 result, without leading to a clinically relevant loss of efficacy, while treatment-related morbidity and mortality were reduced. However, the primary analysis had only limited follow-up, particularly for patients treated with six cycles of eBEACOPP. For this 5-year follow-up analysis, we searched MEDLINE between Jan 1, 2000, and Jan 1, 2021, with the search terms "interim PET" or "PET-2" and "Hodgkin*" to identify studies that assessed the predictive effect of early interim functional imaging with PET-2 in Hodgkin lymphoma. Results from both uncontrolled and controlled studies suggest that PET-2 has a high positive predictive value in advanced-stage Hodgkin lymphoma after upfront ABVD, and that treatment intensification in these patients might be of moderate benefit. The negative predictive value in patients receiving upfront ABVD seems to be less robust.

Added value of this study

This long-term follow-up analysis of the HD18 trial confirms the efficacy of PET-2-guided eBEACOPP, with an acceptable safety profile. The reduction from eight to four cycles of eBEACOPP represents a benchmark in the treatment of early responders with advanced-stage Hodgkin lymphoma, who can now be potentially cured with a short and safe treatment approach. Importantly, as a result of reduced treatment intensity, overall survival was significantly improved. Follow-up data on the secondary outcomes of cardiac and lung toxicity showed no relevant decrease in either treatment group compared with baseline levels. Whereas treatment intensity had no negative impact on the cumulative incidence of childbirth in women aged 18–29 years, an age cutoff of 30 years and older represents a limiting factor for fertility after successful Hodgkin lymphoma treatment. Since the presented data are from several contributing centres in different countries and covering all levels of care, the results of HD18 should be widely applicable in countries with access to FDG-PET for response assessment.

Implications of all the available evidence

The HD18 trial sets the standard for future developments in the treatment of advanced-stage Hodgkin lymphoma, as survival rates with PET-2-guided eBEACOPP exceed any other treatment approach so far while reducing treatment-related morbidity for the majority of patients.

Third Faculty of Medicine, Charles University, Prague, Czech Republic (J Markova MD); **University of Heidelberg, Heidelberg, Germany** (J Meissner MD); **Department of Internal Medicine III, University Hospital of Ulm, Ulm, Germany** (Prof M Feuring-Buske MD); **University of Tübingen, Tübingen, Germany** (M Soekler MD); **University Hospital Mainz, Mainz, Germany** (Prof H-J Beck MD); **Medical University Innsbruck, Internal Medicine V: Hematology & Oncology, Innsbruck, Austria** (W Willenbacher); **Oncotyrol, Center for Personalized Cancer Medicine, Innsbruck, Austria** (W Willenbacher); **HELIOS Medical Center Berlin-Buch, Berlin, Germany** (Prof W-D Ludwig MD); **Department of Medical Oncology, Inselspital Bern, Bern, Switzerland** (Prof T Pabst); **Medizinische Klinik und Poliklinik II, Universitätsklinikum Würzburg, Würzburg, Germany** (Prof M S Topp MD); **Cantonal Hospital of St Gallen, St Gallen, Switzerland** (F Hitz); **Department of Internal Medicine III, Städtisches Klinikum Karlsruhe, Karlsruhe, Germany** (Prof M Bentz MD); **Medical Department, Division of Hematology and Oncology at Campus Benjamin Franklin, Berlin, Germany** (Prof U B Keller MD); **Department of Hematology and Oncology, Charité University of Medicine, Berlin, Germany** (D Kühnhardt MD); **Department of Hematology/Oncology, University Hospital of Munich, Munich, Germany** (Prof H Ostermann MD); **Department of Internal Medicine I, Klinikum Bremen Mitte, Bremen, Germany** (Prof B Hertenstein MD); **Department of Haematology and Oncology, Robert Bosch Hospital, Stuttgart, Germany** (Prof W Aulitzky MD); **Department of Haematology, Oncology and Palliative Care, Ernst von Bergmann Hospital, Potsdam, Germany** (Prof G Maschmeyer MD); **Karl Lennert-Cancer Center, University Hospital Schleswig-Holstein, Kiel, Germany** (T Vieler MD); **Department of Radiotherapy, University Hospital of Münster,**

Münster, Germany (Prof H Eich MD)**; Department of Radiotherapy, University Hospital of Cologne, University of Cologne, Cologne, Germany** (C Baues MD)**; Berlin Reference Center for Lymphoma and Haematopathology, Berlin, Germany** (Prof H Stein MD)

Correspondence to: Prof P Borchmann, First Department of Internal Medicine, German Hodgkin Study Group, University Hospital of Cologne, D-50924 Cologne, Germany
peter.borchmann@uk-koeln.de

In this prespecified analysis, we report long-term follow-up data up to 5 years for the entire study cohort to further evaluate the efficacy and safety of PET-guided eBEACOPP in advanced-stage Hodgkin lymphoma. For patients with a positive PET-2 result, we added an updated 5-year description of the non-randomised post-amendment subgroup receiving six cycles of eBEACOPP. In patients with a negative PET-2 result who were randomly assigned after the protocol amendment, we assessed whether the previously published findings of the HD18 study[11] also hold true when six cycles of eBEACOPP are considered as standard therapy. Finally, we complemented the efficacy results with long-term safety data, including information about lung and cardiac function as well as fertility.

Methods

Study design and participants

HD18 was an international, open-label, randomised, phase 3 trial done in 301 hospitals and private practices in Germany, Switzerland, Austria, the Netherlands, and the Czech Republic (appendix 2 pp 21–27). The protocol and statistical analysis plan are included at the end of appendix 2. All patients provided written informed consent before enrolment. The trial was approved by the ethics committees of all participating sites and done in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.

See Online for appendix 2

Patients aged 18–60 years with newly diagnosed Hodgkin lymphoma of any histological subtype in advanced stage (ie, clinical stage II with B symptoms and one or both risk factors of a large mediastinal mass [at least a third of the maximal thoracic diameter] or extranodal lesions, or clinical stage III or IV) and an Eastern Cooperative Oncology Group performance status of 0–2 were eligible for inclusion in the study. Other inclusion criteria were HIV negativity and freedom from concurrent disease that would preclude treatment according to the protocol. Further details of the study design and eligibility criteria have been published and are summarised in appendix 2 (pp 1–2).[11]

Randomisation and masking

Randomisation was done centrally at the German Hodgkin Study Group Trial Coordination Center with the minimisation method, including a random component, stratified according to centre, age (<45 years *vs* ≥45 years), stage (IIB–IIIA *vs* IIIB–IV), international prognostic score (0–2 *vs* 3–7), and sex.[11] Patients and investigators were not masked to treatment allocation.

Procedures

Procedures are summarised in appendix 2 (pp 3–4).[11] All patients received two cycles of eBEACOPP followed by a restaging including contrast-enhanced CT and a PET scan (PET-2). After central review of PET-2, patients were randomly assigned (1:1) to one of two parallel treatment groups on the basis of their PET-2 result. PET-2 with ^{18}F-FDG uptake higher than the mediastinal blood pool (ie, a Deauville score of ≥3) was considered as positive.

Patients with positive PET-2 were randomly assigned to receive either six additional cycles of eBEACOPP (ie, eight cycles of eBEACOPP in total) or six cycles of eBEACOPP plus rituximab until a protocol amendment on June 1, 2011. With this amendment, standard therapy was reduced from eight to six cycles of eBEACOPP, on the basis of the results of our HD15 trial.[1] After June 1, 2011, all patients with positive PET-2 were assigned to treatment with the updated standard therapy of six cycles of eBEACOPP in total, while enrolment in the group assigned to receive eight cycles of rituximab plus eBEACOPP was stopped because the required sample size for the superiority test had already been reached. Patients with negative PET-2 were randomly assigned to receive standard therapy, initially with six additional cycles of eBEACOPP (ie, eight cycles of eBEACOPP in total), or experimental therapy with two additional cycles of eBEACOPP (ie, four cycles of eBEACOPP in total). After the protocol amendment on June 1, 2011, treatment in the standard therapy group was reduced to six cycles in total, while the experimental treatment remained unchanged. In all four groups, radiotherapy was recommended for lesions of at least 2·5 cm in the largest diameter with residual ^{18}F-FDG uptake after chemotherapy.

Patients were followed up for at least 5 years within the study. Patients providing separate, written, informed consent were followed up until the end of the study, which was scheduled 5 years after end of enrolment. The study ended with the last visit of the last patient on July 18, 2019. During the follow-up period, physical examinations, laboratory tests, chest X-ray, pulmonary function, abdominal ultrasound, thyroid diagnostics, electrocardiography and echocardiography, assessment of gonadal function, and self-assessment of quality of life were requested at the following intervals: every 3 months in the first year, every 6 months in the second to fourth year, and once a year thereafter. Provided a complete response had been reached, CT scans were to be done only in cases of suspected tumour recurrence.

Outcomes

The primary endpoint was progression-free survival, defined as the time from completion of staging until progression, relapse, or death from any cause. If none of these events had occurred, progression-free survival was censored at the date of the last information on disease status.

Secondary endpoints reported in this follow-up analysis were overall survival (defined as the time from completion of staging until death from any cause, or censored at the date of last information on the patient being alive), time to first occurrence of second primary malignant neoplasm

(defined as the time from completion of staging until first second primary malignant neoplasm diagnosis or censored at the date of last information on disease status, accounting for death as a competing risk), cardiac function (in terms of mean left ventricular ejection fraction) and lung function (in terms of mean diffusion capacity of the lung) after 5 years of follow-up, time to first childbirth (defined in female patients as the time from end of therapy until the day of birth of the first child born after therapy, or censored at the date of last information on disease status, accounting for death, second primary malignant neoplasm, and disease recurrence as competing risks), and second progression-free survival (prespecified in the statistical analysis plan for this follow-up analysis, and defined as the time from diagnosis of first progression or relapse until further documented relapse or death from any cause, or censored at the date of last information on disease status). Additional secondary endpoints were the proportion of patients with a complete response and treatment-related adverse events, which have already been published,[11] as well as quality of life, which will be published separately.

Statistical analysis

In this follow-up analysis, we repeated the primary superiority analysis of progression-free survival for PET-2-positive patients and the primary non-inferiority analysis for PET-2-negative patients, and report the pre-planned subgroup analyses of patients recruited after the protocol amendment on June 1, 2011. Details about sample size calculations have been published[11] and are summarised in appendix 2 (p 2).

For PET-2-positive patients, the primary objective was to show the superiority of rituximab plus eBEACOPP over eBEACOPP in terms of progression-free survival among patients randomly assigned before the protocol amendment was in effect (ie, enrolled before June 1, 2011).[11,12] The study in patients with positive PET-2 was designed to detect an improvement of at least 15% in 5-year progression-free survival with a power of 80% and a two-sided significance level of 5%. For patients assigned to receive six cycles of eBEACOPP after the protocol amendment, we did a descriptive analysis of primary and secondary endpoints as well as pre-planned subgroup analyses of progression-free survival and overall survival by Deauville score (3 *vs* 4).

In the PET-2-negative cohort, the primary objective was to show the non-inferiority of the shortened treatment compared with standard treatment in terms of progression-free survival. Clinically relevant inferiority of four cycles of eBEACOPP was defined as an absolute difference of 6% or more in the 5-year progression-free survival estimates. Non-inferiority would be established if the lower limit of the two-sided 95% CI for the difference between eight or six cycles and four cycles of eBEACOPP in the 5-year progression-free survival estimates was higher than –6%.[11] We repeated the analysis of pooled pre-amendment and post-amendment cohorts as done in the primary analysis and added a pre-planned post-amendment subgroup analysis using the same non-inferiority margin.

The secondary endpoints of overall survival, second progression-free survival, and cumulative incidence of second primary malignant neoplasms were analysed in the PET-2-positive and PET-2-negative cohorts as well as in the respective post-amendment subgroups by assigned treatment group.

Lung and cardiac function were analysed by assigned treatment group separately for male and female patients without differentiation between PET-2 results or enrolment period (pre-amendment or post-amendment) in a complete case analysis. Fertility outcomes were analysed by assigned treatment group in the following pre-defined subgroups defined by sex and age at enrolment: male patients aged 18–60 years, female patients aged 18–29 years, and female patients aged 30–40 years. We also did pre-planned subgroup analyses of female patients with documented pre-treatment cryopreservation, assuming that the decision for cryopreservation might reflect a woman's wish to have children after successful Hodgkin lymphoma treatment.

We compared time-to-event endpoints using the Kaplan-Meier method, including hazard ratios (HRs) and 95% CIs obtained from Cox regression models and log-rank tests where applicable. Other analyses were done with descriptive statistics.

As done in the primary analysis, progression-free survival and overall survival in the PET-2-negative cohort were primarily analysed per protocol, and sensitivity analyses as well as all other analyses were done according to the intention-to-treat (ITT) principle, whereby analysis sets remained unchanged from the primary analysis:[11] the ITT set excluded all patients whose diagnosis of Hodgkin lymphoma was disconfirmed by the pathology review panel, those with registration errors, and those who withdrew their consent to participate in the trial, while the per-protocol set additionally excluded all patients with severe protocol deviations, violation of inclusion criteria, or missing documentation of study therapy. Importantly, analyses within the PET-2-positive or PET-2-negative cohorts only included patients who were assigned to a treatment group on the basis of their centrally reviewed PET-2 result. We used SAS, version 9.4, for all analyses.

This trial is registered with ClinicalTrials.gov, NCT00515554, and is completed.

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between May 14, 2008, and July 18, 2014, 2101 patients were enrolled and 1945 were assigned to a treatment group according to their PET-2 result (figure 1). Local and central assessment of PET positivity or negativity

was concordant in 1541 (80%) of 1936 patients (information missing in nine of 1945 patients). Agreement was stronger among patients who were considered PET-negative by central review (897 [90%] of 1000 patients) or clearly PET-positive (366 [78%] of 468 patients with Deauville score 4) by central review, than in those with a Deauville score of 3 (278 [59%] of 468 patients).

Patient's baseline characteristics were similar between the randomised treatment groups (appendix 2 pp 5–7).[11]

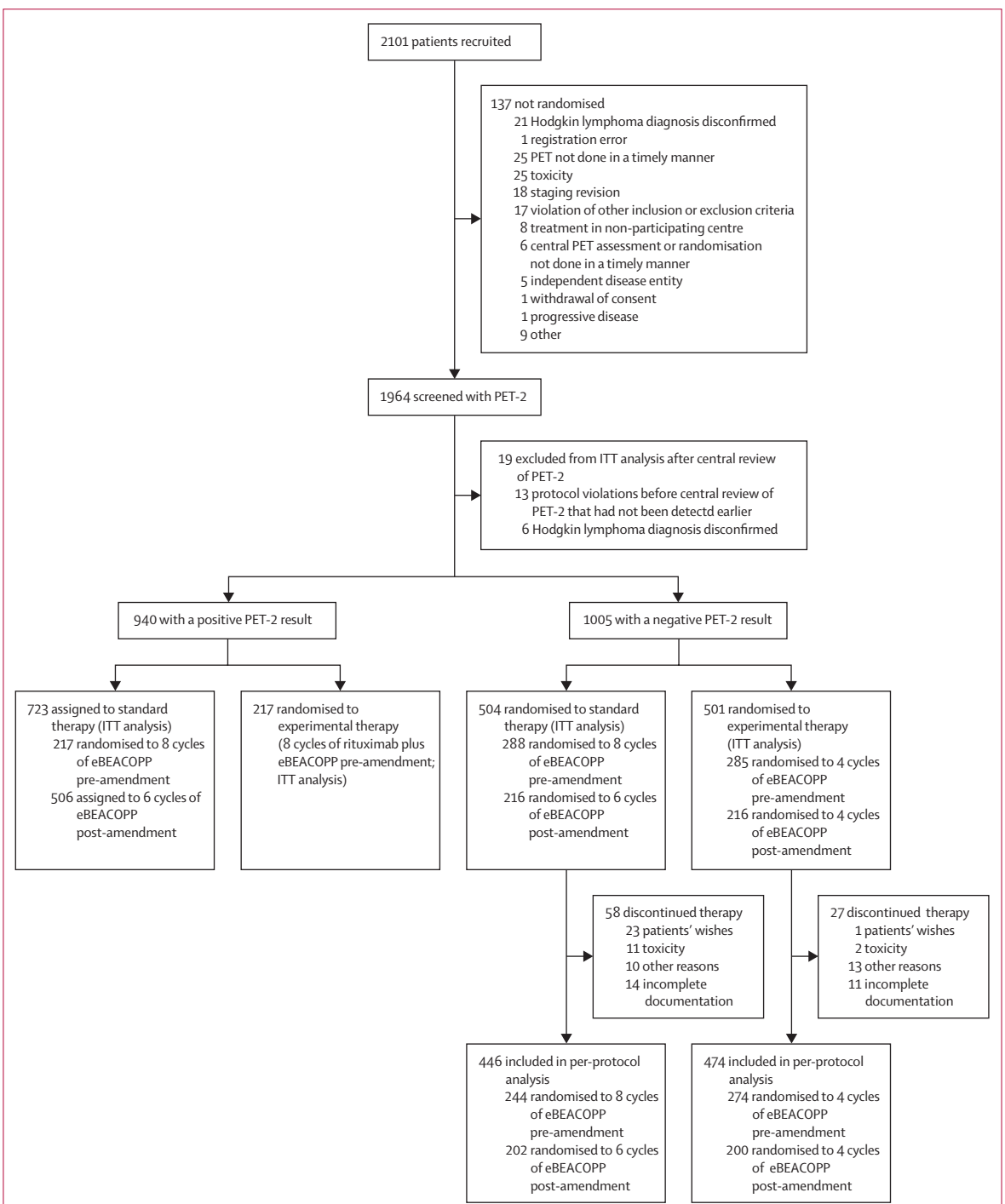

Figure 1: **Trial profile**
The date of the protocol amendment was June 1, 2011. eBEACOPP=bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and procarbazine in escalated doses. ITT=intention-to-treat. PET-2=PET scan after two cycles of chemotherapy.

In the PET-2-positive cohort randomly assigned before the protocol amendment, with a median follow-up of 73 months (IQR 59–94), estimated 5-year progression-free survival was 89·9% (95% CI 85·7–94·1) with eight cycles of eBEACOPP and 87·7% (83·1–92·4) with eight cycles of rituximab plus eBEACOPP (log-rank p=0·40; appendix 2 p 8). Second progression-free survival after 2 years was 73·8% (95% CI 48·2–99·5) in 14 patients who progressed or relapsed after eight cycles of eBEACOPP and 41·5% (16·4–66·5) among 17 patients who were assigned to receive eight cycles of rituximab plus eBEACOPP (p=0·12; appendix 2 p 8). After a median follow-up for survival of 78 months (IQR 62–99), nine patients assigned to eight cycles of eBEACOPP had died, as had 16 patients assigned to eight cycles of rituximab plus eBEACOPP, including one death from Hodgkin lymphoma in each group (table 1), corresponding to a 5-year overall survival of 96·5% (95% CI 94·0–99·1) with eight cycles of eBEACOPP and 93·4% (90·0–96·9) with eight cycles of rituximab plus eBEACOPP (log-rank p=0·15; appendix 2 p 9). After 5 years, the cumulative incidence of second primary malignant neoplasms was 4·0% (95% CI 1·3–6·7) with eight cycles of eBEACOPP and 3·3% (0·7–5·9) with eight cycles of rituximab plus eBEACOPP (p=0·44; appendix 2 p 9).

Among 506 PET-2-positive patients assigned to six cycles of eBEACOPP after the protocol amendment, the estimated 5-year progression-free survival was 90·1% (95% CI 87·2–92·9; appendix 2 p 10), with a median follow-up of 58 months (IQR 39–66). Second progression-free survival at 2 years was 76·0% (95% CI 58·7–93·3) in 34 patients who progressed or relapsed (table 1; appendix 2 p 10). At the time of analysis, 15 patients had died, including three deaths from Hodgkin lymphoma (table 1). The estimated 5-year overall survival was 96·7% (95% CI 94·9–98·4; appendix 2 p 11). The cumulative incidence of second primary malignant neoplasms after 5 years was 4·6% (95% CI 2·6–6·7; appendix 2 p 11).

Among patients with positive PET-2 assigned to six cycles of eBEACOPP, a Deauville score of 4 was associated with significantly poorer progression-free survival than a Deauville score of 3 (5-year estimate: 85·6% [95% CI 80·8–90·5] *vs* 94·1% [90·9–97·3]; log-rank p=0·0014); similar results were observed for overall survival (94·5% [95% CI 91·3–97·7] *vs* 98·6% [97·1–100·0]; log-rank p=0·011; appendix 2 p 12).

With a median follow-up for disease status of 66 months (IQR 54–85) in the combined pre-amendment and post-amendment PET-2-negative cohort, the estimated 5-year progression-free survival was 91·2% (95% CI 88·4–93·9) with eight or six cycles of eBEACOPP and 93·0% (90·6–95·4) with four cycles of eBEACOPP in the per-protocol analysis (difference 1·9% [–1·8 to 5·5]; appendix 2 p 13). With a 95% CI for the 5-year difference thus excluding the predefined margin of –6%, non-inferiority of the shorter treatment could be confirmed.

Second progression-free survival after 2 years was 63·9% (95% CI 44·6–83·1) for the 29 patients who progressed or relapsed after eight or six cycles of eBEACOPP and 65·7% (48·4–83·0) for the 34 patients who progressed or relapsed after four cycles of eBEACOPP (table 2; appendix 2 p 15). The majority of these patients

	PET-2-positive cohort pre-amendment		PET-2-positive cohort post-amendment
	8 cycles of eBEACOPP (n=217)	8 cycles of rituximab plus eBEACOPP (n=217)	6 cycles of eBEACOPP (n=506)
Follow-up			
Follow-up for disease status, months	75 (60–94)	72 (56–94)	58 (39–66)
Follow-up for survival status, months	77 (64–98)	79 (61–101)	60 (46–71)
Tumour events			
Any tumour event	14 (6%)	17 (8%)	34 (7%)
Progression	1 (<1%)	4 (2%)	7 (1%)
Early relapse (within 1 year after end of treatment)	6 (3%)	5 (2%)	11 (2%)
Late relapse	7 (3%)	8 (4%)	16 (3%)
Number of tumour events			
1	11 (5%)	12 (6%)	29 (6%)
2	1 (<1%)	3 (1%)	4 (1%)
3	2 (1%)	2 (1%)	1 (<1%)
Second-line therapy			
High-dose chemotherapy and autologous HSCT	12 (6%)	9 (4%)	17 (3%)
Allogeneic HSCT	1 (<1%)	0	1 (<1%)
Salvage chemotherapy without documented HSCT	0	7 (3%)	2 (<1%)
Other chemotherapy	0	1 (<1%)	0
Radiotherapy only	0	0	4 (1%)
Antibody therapy	0	0	2 (<1%)
Unknown	1 (<1%)	0	8 (2%)
Cause of death			
Any event	9 (4%)	16 (7%)	15 (3%)
Hodgkin lymphoma	1 (<1%)	1 (<1%)	3 (1%)
Toxicity of study treatment	1 (<1%)	4 (2%)	0
Toxicity of salvage therapy	3 (1%)	3 (1%)	1 (<1%)
Second primary malignant neoplasms	2 (1%)	3 (1%)	7 (1%)
Other disease*	2 (1%)	3 (1%)	1 (<1%)
Accident or suicide	0	2 (1%)	0
Unclear	0	0	3 (1%)
Second primary malignant neoplasms			
Any event	12 (6%)	8 (4%)	22 (4%)
Acute myeloid leukaemia or myelodysplastic syndrome	5 (2%)	4 (2%)	5 (1%)
Non-Hodgkin lymphoma	3 (1%)	2 (1%)	8 (2%)
Solid tumour	6 (3%)	2 (1%)	9 (2%)

Data are median (IQR) or n (%). PET-2=PET scan after two cycles of chemotherapy. eBEACOPP=bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone in escalated doses. HSCT=haematopoietic stem-cell transplantation. *Including non-treatment-related infection (n=4) and non-treatment-related pulmonary disease (n=2).

Table 1: **Outcomes of the PET-2-positive cohort**

received second-line treatment with high-dose chemotherapy and autologous haematopoietic stem-cell transplantation (table 2). Among 63 patients who progressed or relapsed, 15 had died at the time of the analysis: eight assigned to eight or six cycles of eBEACOPP (four due to Hodgkin lymphoma, two due to treatment-related complications, and two due to a second primary malignant neoplasm) and seven assigned to four cycles of eBEACOPP (five due to Hodgkin lymphoma and two due to treatment-related complications).

Causes of death are summarised in table 2. Overall survival at 5 years was 95·3% (95% CI 93·3–97·3) with eight or six cycles of eBEACOPP and 98·1% (96·8–99·4) with four cycles of eBEACOPP in the per-protocol analysis and thus still indicated a significant advantage of the shorter treatment regimen (log-rank p=0·0038; appendix 2 p 13). The overall survival difference between eight or six cycles of eBEACOPP and four cycles of eBEACOPP was mainly based on deaths from second primary malignant neoplasms and treatment-related toxicities (table 2).

	PET-2-negative cohort, pre-amendment		PET-2-negative cohort, post-amendment		PET-2-negative cohort, combined	
	8 cycles of eBEACOPP (n=288)	4 cycles of eBEACOPP (n=285)	6 cycles of eBEACOPP (n=216)	4 cycles of eBEACOPP (n=216)	8 or 6 cycles of eBEACOPP (n=504)	4 cycles of eBEACOPP (n=501)
Follow-up						
Follow-up for disease status, months	76 (61–96)	75 (60–97)	59 (47–70)	57 (43–64)	66 (54–86)	64 (51–84)
Follow-up for survival status, months	83 (64–101)	78 (63–101)	60 (52–75)	61 (50–69)	69 (56–90)	66 (54–88)
Tumour events						
Any tumour event	16 (6%)	19 (7%)	13 (6%)	15 (7%)	29 (6%)	34 (7%)
Progression	1 (<1%)	0	0	3 (1%)	1 (<1%)	3 (1%)
Early relapse (within 1 year after end of treatment)	3 (1%)	7 (2%)	4 (2%)	5 (2%)	7 (1%)	12 (2%)
Late relapse	12 (4%)	12 (4%)	9 (4%)	7 (3%)	21 (4%)	19 (4%)
Number of tumour events						
1	15 (5%)	18 (6%)	11 (5%)	12 (6%)	26 (5%)	30 (6%)
2	1 (<1%)	1 (<1%)	1 (<1%)	3 (1%)	2 (<1%)	4 (1%)
3	0	0	1 (<1%)	0	1 (<1%)	0
Second-line therapy						
High-dose chemotherapy and autologous HSCT	9 (3%)	8 (3%)	7 (3%)	10 (5%)	16 (3%)	18 (4%)
Allogeneic HSCT	0	1 (<1%)	0	0	0	1 (<1%)
Salvage chemotherapy without documented HSCT	3 (1%)	3 (1%)	2 (1%)	1 (<1%)	5 (1%)	4 (1%)
Other chemotherapy	2 (1%)	2 (1%)	1 (<1%)	1 (<1%)	3 (1%)	3 (1%)
Radiotherapy only	1 (<1%)	1 (<1%)	0	0	1 (<1%)	1 (<1%)
Antibody therapy	1 (<1%)	0	0	1 (<1%)	1 (<1%)	1 (<1%)
Unknown	0	4 (1%)	3 (1%)	2 (1%)	3 (1%)	6 (1%)
Cause of death						
Any event	19 (7%)	6 (2%)	9 (4%)	5 (2%)	28 (6%)	11 (2%)
Hodgkin lymphoma	2 (1%)	3 (1%)	2 (1%)	2 (1%)	4 (1%)	5 (1%)
Toxicity of study treatment	4 (1%)	0	2 (1%)	0	6 (1%)	0
Toxicity of salvage therapy	2 (1%)	1 (<1%)	0	1 (<1%)	2 (<1%)	2 (<1%)
Second primary malignant neoplasms	8 (3%)	1 (<1%)	5 (2%)	1 (<1%)	13 (3%)	2 (<1%)
Other disease*	1 (<1%)	0	0	1 (<1%)	1 (<1%)	1 (<1%)
Accident or suicide	0	1 (<1%)	0	0	0	1 (<1%)
Unclear	2 (1%)	0	0	0	2 (<1%)	0
Second primary malignant neoplasms						
Any event	14 (5%)	12 (4%)	7 (3%)	6 (3%)	21 (4%)	18 (4%)
Acute myeloid leukaemia or myelodysplastic syndrome	7 (2%)	1 (<1%)	2 (1%)	1 (<1%)	9 (2%)	2 (<1%)
Non-Hodgkin lymphoma	3 (1%)	6 (2%)	2 (1%)	2 (1%)	5 (1%)	8 (2%)
Solid tumour	5 (2%)	5 (2%)	3 (1%)	3 (1%)	8 (2%)	8 (2%)

Data are median (IQR) or n (%). PET-2=PET scan after two cycles of chemotherapy. eBEACOPP=bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone in escalated doses. HSCT=haematopoietic stem-cell transplantation. *Including diarrhoea (n=1) and non-treatment-related infection (n=1).

Table 2: **Outcomes of the PET-2-negative cohort**

Within the observed follow-up period, a second primary malignant neoplasm occurred in 21 patients assigned to eight or six cycles of eBEACOPP, corresponding to a 5-year cumulative incidence of 3·7% (95% CI 2·0–5·4), and in 18 patients assigned to four cycles of eBEACOPP, corresponding to a 5-year cumulative incidence of 3·3% (1·6–5·0; p=0·66; appendix 2 p 15). The types of second primary malignant neoplasms are summarised in table 2.

In the subgroup of PET-2-negative patients who were randomly assigned after standard treatment had changed from eight to six cycles in 2011, the estimated 5-year progression-free survival was 90·9% (95% CI 86·8–95·1) with six cycles of eBEACOPP and 91·0% (86·6–95·5) with four cycles of eBEACOPP (figure 2A), with a median follow-up of 58 months (IQR 47–67) in the per-protocol analysis. With a 95% CI for the 5-year difference ranging from –5·9% to 6·2% and thus entirely exceeding the predefined non-inferiority margin of –6%, the non-inferiority of the shorter treatment could be established in this subgroup. After a median follow-up of 61 months (IQR 51–71), the estimated 5-year overall survival was 96·3% (95% CI 93·7–99·0) with six cycles of eBEACOPP and 97·5% (95·0–100·0) with four cycles of eBEACOPP (log-rank p=0·18; figure 2B) and thus more similar between these treatment groups compared with the combined pre-amendment and post-amendment analysis. Accordingly, the difference in reported deaths was less pronounced, with second primary malignant neoplasms and treatment-related morbidity remaining the leading causes (table 2). The 5-year cumulative incidence of second primary malignant neoplasms was 3·1% (95% CI 0·6–5·6) with six cycles of eBEACOPP and 2·9% (0·3–5·5) with four cycles of eBEACOPP (appendix 2 p 17).

ITT results for progression-free survival and overall survival of PET-2-negative patients are summarised in appendix 2 (pp 14–16).

5-year estimates for the entire ITT study cohort were 90·1% (95% CI 88·7–91·5) for progression-free survival, with a median follow-up of 64 months (IQR 49–82), and 95·8% (94·9–96·7) for overall survival, with a median follow-up of 66 months (53–87; appendix 2 p 18).

The secondary outcomes of cardiac and lung toxicity after 5 years of follow-up, mean left ventricular ejection fraction and diffusion capacity of the lung, are summarised in table 3.

45 (4%) of 1105 male patients reported childbirth after the end of study treatment, within a median observation time of 65 months (IQR 53–85) after the end of therapy. In 37 (82%) of these patients, sperm cryopreservation had been done before chemotherapy. However, information about whether cryogenic material had been used was only available in 16 patients, of whom one (6%) reported having used cryogenic material.

Of 330 female patients aged 18–29 years at enrolment, 59 (18%) reported a successful pregnancy within a median observation time of 66 months (IQR 56–84) after the end of therapy. 5-year estimates for first childbirth after therapy reached similar levels irrespective of treatment intensity: 18·0% (95% CI 11·0–25·1) after eight cycles of eBEACOPP, 17·7% (9·5–25·9) after six cycles of eBEACOPP, and 15·3% (6·4–24·1) after four cycles of eBEACOPP (appendix 2 p 19). Among 197 women aged 30–40 years, 14 (7%) reported successful pregnancies within a median observation time of 66 months (IQR 55–85). 5-year estimates for first childbirth were descriptively lower in patients assigned to eight cycles of eBEACOPP (6·0%; 95% CI 0·0–12·6) than in those assigned to six cycles of eBEACOPP

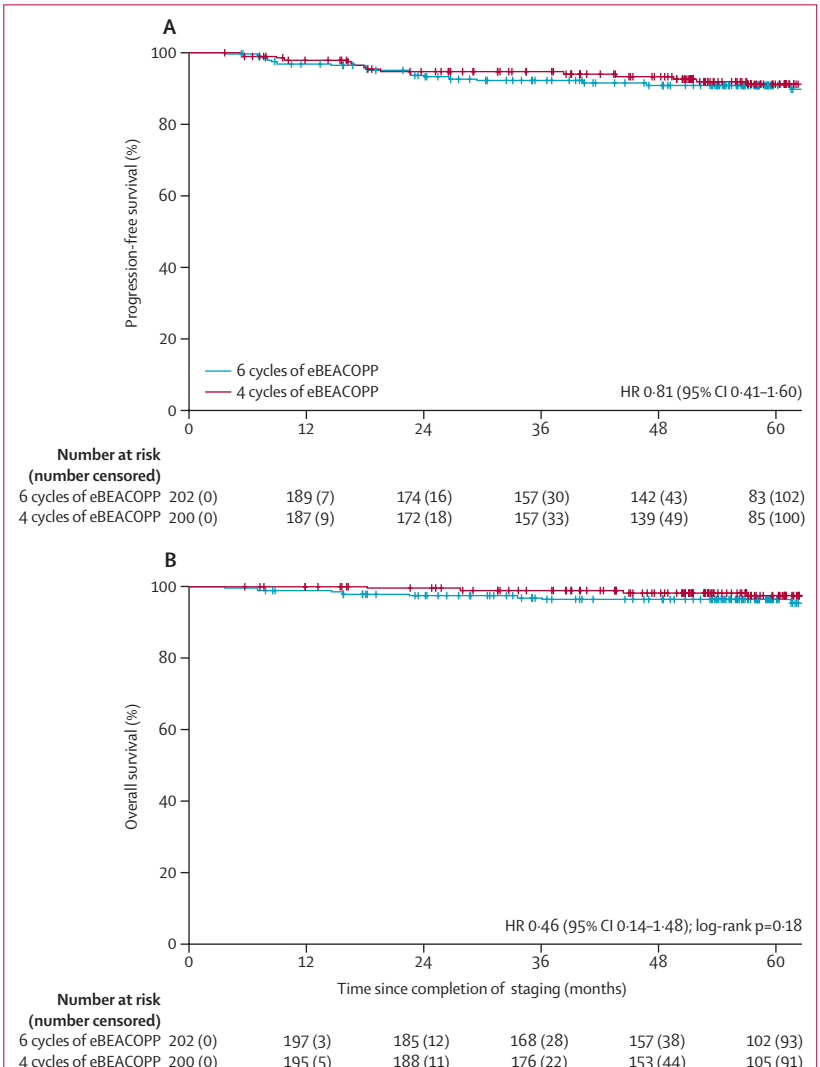

Figure 2: **Kaplan-Meier estimates in the post-amendment PET-2-negative per-protocol cohort**
(A) Progression-free survival. 5-year progression-free survival estimates: 90·9% (95% CI 86·8 to 95·1) with six cycles of eBEACOPP and 91·0% (86·6 to 95·5) with four cycles of eBEACOPP; difference 0·1% (–5·9 to 6·2). (B) Overall survival. 5-year overall survival estimates: 96·3% (95% CI 93·7 to 99·0) with six cycles of eBEACOPP and 97·5% (95·0 to 100·0) with four cycles of eBEACOPP; difference 1·1% (–2·5 to 4·8). eBEACOPP=bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and procarbazine in escalated doses. HR=hazard ratio. PET-2=PET scan after two cycles of chemotherapy.

	8 cycles of eBEACOPP or 8 cycles of rituximab plus eBEACOPP		6 cycles of eBEACOPP		4 cycles of eBEACOPP		Total	
	Number of participants	Mean (SD)	Number of participants	Mean (SD)	Number of participants	Mean (SD)	Number of participants	Mean (SD)
Female patients								
Cardiac function								
LVEF (baseline), all available data	210	64·7% (8·6)	211	63·5% (7·7)	156	65·2% (8·4)	577	64·4% (8·2)
LVEF (baseline), only patients with follow-up data	35	64·5% (8·9)	32	62·5% (6·1)	26	65·4% (9·3)	93	64·1% (8·2)
LVEF (5-year follow-up)	35	62·8% (10·2)	32	62·3% (6·0)	26	62·3% (6·5)	93	62·5% (7·9)
Lung function								
DLCO (baseline), all available data	142	75·9% (15·9)	166	78·4% (19·8)	101	80·6% (17·8)	409	78·1% (18·1)
DLCO (baseline), only patients with follow-up data	14	73·2% (15·2)	15	79·2% (25·5)	4	78·2% (40·7)	33	76·5% (23·3)
DLCO (5-year follow-up)	14	78·1% (9·7)	15	70·1% (27·1)	4	84·1% (17·2)	33	75·2% (20·3)
Male patients								
Cardiac function								
LVEF (baseline), all available data	313	63·5% (7·1)	351	63·4% (6·8)	246	63·8% (7·1)	910	63·5% (7·0)
LVEF (baseline), only patients with follow-up data	55	64·4% (6·9)	61	64·0% (6·6)	41	63·7% (6·8)	157	64·1% (6·7)
LVEF (5-year follow-up)	55	61·3% (8·5)	61	61·5% (5·4)	41	60·3% (5·9)	157	61·1% (6·7)
Lung function								
DLCO (baseline), all available data	232	82·6% (19·7)	243	81·2% (24·4)	172	81·3% (21·6)	647	81·8% (22·1)
DLCO (baseline), only patients with follow-up data	15	79·5% (17·1)	14	89·5% (10·9)	8	90·1% (13·4)	37	85·6% (14·8)
DLCO (5-year follow-up)	15	84·7% (12·1)	14	82·5% (24·7)	8	87·4% (17·5)	37	84·5% (18·4)

Data are n or mean (SD). eBEACOPP=bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone in escalated doses. LVEF=left ventricular ejection fraction. DLCO=diffusion capacity of the lung.

Table 3: **Secondary outcomes of cardiac and lung toxicities**

(10·9%; 1·8–19·9) and those assigned to four cycles of eBEACOPP (12·9%; 1·9–23·9; appendix 2 p 19).

Cryopreservation before chemotherapy was documented in 27 (36%) of 74 women who later had children. However, no information about the usage of cryogenic material was available. In women who underwent pretreatment cryopreservation, 5-year estimates for first childbirth were 12·7% (95% CI 5·9–19·5) in women aged 18–29 years compared to 36·5% (16·3–56·7) in women aged 30–40 years (appendix 2 p 20).

Discussion

This long-term follow-up analysis of the HD18 trial confirms the efficacy and acceptable safety profile of PET-2-guided eBEACOPP for patients with advanced-stage Hodgkin lymphoma. After a positive PET-2, 5-year progression-free survival was higher than 90% with the updated standard of care of six cycles of eBEACOPP, indicating the importance of intensive first-line therapy for high-risk patients. In the PET-2-negative cohort, our follow-up analysis established the non-inferiority of four cycles of eBEACOPP compared to both eight and six cycles of eBEACOPP in terms of progression-free survival, which translated into overall survival higher than 95% after 5 years.

The German Hodgkin Study Group's treatment strategy involving eBEACOPP as first-line regimen is inspired by the Kairos principle, reflecting the importance of definite upfront lymphoma control, which should be reached by elimination of refractoriness to chemotherapy, to achieve long-term remission. Based on this principle, intensification of first-line therapy from the established ABVD regimen towards the more intensive eBEACOPP has been tested in several large prospective randomised trials and has shown the highest probability of patients remaining free from disease recurrence.[1,2,13–18] Potentially being cured of Hodgkin lymphoma and thereby avoiding further toxic treatments is considered the most important aspect in the choice of treatment for the vast majority of patients.[19,20] However, given the acute and long-term toxicity of eBEACOPP, further individualisation of treatment is needed, primarily to avoid overtreatment in low-risk patients while maintaining favourable survival outcomes. These considerations formed the rationale behind the HD18 trial.

The addition of rituximab to chemotherapy in the HD18 trial did not improve progression-free survival of patients with positive PET-2, and eBEACOPP remained the standard of care for this subgroup.[11] Importantly, 5-year progression-free survival in PET-2-positive patients was better than expected in both treatment groups (ie, with or without rituximab), reaching higher than 85% after 5 years in this presumably high-risk cohort.

Among patients with positive PET-2 enrolled after the protocol amendment on June 1, 2011, who received the updated standard treatment of six cycles of eBEACOPP, estimated 5-year progression-free survival remained excellent, at 90·1%. Even in patients with a Deauville score

of 4, a 5-year progression-free survival of 85·6% (95% CI 80·8–90·5) still exceeded the 3-year outcome of patients escalated to eBEACOPP after two cycles of upfront ABVD in the RATHL trial.[17] Six cycles of eBEACOPP resulted in high tumour control and an improved safety profile compared to the former standard of eight cycles. Therefore, six cycles remain the German Hodgkin Study Group's standard of care for patients with advanced-stage Hodgkin lymphoma and a positive PET-2 result.

The primary results of the HD18 trial in 2017 showed that a negative PET scan after initial therapy with two cycles of eBEACOPP allows a substantial reduction of treatment from initially eight to four cycles without having a negative impact on progression-free survival.[11] In our current analysis, with follow-up of 66 months, we observed that the non-inferiority of four cycles of eBEACOPP, in terms of progression-free survival, persisted. The shorter treatment was also non-inferior to the more tolerable newer standard of six cycles.

Acute treatment-related toxicity was reduced from 66% with eight cycles of eBEACOPP to 41% with four cycles of eBEACOPP, as previously shown.[11] In our analysis, reduced treatment with four cycles of eBEACOPP was still associated with a significant overall survival benefit when compared with eight or six cycles of eBEACOPP. However, this overall survival benefit was mainly attributed to the comparison with the former standard of eight cycles of eBEACOPP, and was less pronounced in comparison with six cycles of eBEACOPP. Notably, no treatment-related deaths were observed with four cycles of eBEACOPP. The leading cause of death in the group assigned to receive eight or six cycles of eBEACOPP was second primary malignant neoplasms, while deaths related to second primary malignant neoplasms were rare with four cycles of eBEACOPP. Nine of 21 second primary malignant neoplasms reported among patients treated with eight or six cycles of eBEACOPP were myelodysplastic syndrome or acute myeloid leukaemia. The association between exposure to high-dose alkylating drugs as well as topoisomerase II inhibitors and an increased risk of therapy-related acute myeloid leukaemia is now well established.[3,21–23] By reducing the cumulative treatment intensity to four cycles of eBEACOPP, we saw a clinically relevant decrease in the incidence of myelodysplastic syndrome or acute myeloid leukaemia, which is in line with published data for less intensive treatment strategies such as the ABVD regimen.[3,13–17,24]

Results for cardiac and lung toxicity, in terms of mean left ventricular ejection fraction and diffusion capacity of the lung, were similar between all treatment groups and, importantly, there was no clinically relevant decrease in either group compared with baseline levels. Although information about cardiac and lung toxicity was only available for a small subset of patients, the findings underscore the safety of the overall treatment strategy of eBEACOPP, representing an important criterion for newly diagnosed patients who do not yet know whether they will receive four or six cycles. Importantly, even patients receiving six cycles of eBEACOPP are exposed to considerably lower cumulative doses of doxorubicin and bleomycin than those treated with six cycles of ABVD.

Among treatment-related sequelae, infertility is of particular importance in Hodgkin lymphoma survivors. In our analysis, the proportion of pre-treatment cryopreservations was higher in male patients than in female patients. As a limiting factor, information about how many children were born as a result of the use of cryogenic material was not available. Furthermore, the numbers of patients who had children after therapy might be underestimated, particularly for male patients, as not all pregnancies of a patient's partner might have been assessed by use of standard follow-up documentation, which was not particularly suited towards fertility assessment.

With regard to the time to first childbirth, 5-year estimates in female survivors aged 18–29 years were higher than in women aged 30–40 years. In younger women, no differences based on treatment intensity were observed, whereas older women showed lower 5-year estimates after eight cycles of eBEACOPP than after six or four cycles. An age cutoff of 30 years or older has previously been reported to have a stronger negative impact on the risk of sustained amenorrhea and reduced ovarian reserve after treatment for advanced-stage Hodgkin lymphoma than treatment intensity itself.[25] Additionally, family planning in younger women (<30 years) is presumably more often not yet completed at the time of diagnosis, which might also contribute to higher birth rates in younger women. However, birth rates should generally be correlated with patients' desires for having children, and this information was not assessed in the HD18 trial. We evaluated the subgroup of women with documented pre-treatment cryopreservation, assuming that this decision might reflect women's wishes to have children after successful Hodgkin lymphoma treatment. In this subgroup analysis, 5-year estimates in women aged 30 years and older were higher than in women younger than 30 years, indicating that older women tend to get pregnant earlier after the end of treatment in case their family planning is not yet completed. In principle, birth rates in patients with a desire for having children represent an appropriate endpoint for evaluation of fertility in cancer survivors, particularly because hormone levels do not always reliably predict infertility in individual patients.[26] In general, to maintain the chances of assisted reproduction after treatment for Hodgkin lymphoma, cryopreservation should routinely be offered to all male and female patients at the time of diagnosis, with a particular focus on women aged 30 years or older, since age represents a limiting factor for fertility after successful Hodgkin lymphoma treatment.

Following the PET-guided eBEACOPP strategy, about a third of patients need more than four cycles of treatment.[11] In view of the particularly young age at first diagnosis of

most patients with Hodgkin lymphoma, both acute and long-term toxicities of eBEACOPP remain a matter of concern. When considering future de-escalation strategies to reduce toxicity on one hand but preserve the efficacy of eBEACOPP on the other hand, further PET-guided reduction of the number of treatment cycles needed to reach complete remission might be a more effective strategy than reducing the intensity of each cycle while maintaining their cumulative number.

Through implementation of new and less genotoxic drugs into the classical chemotherapy backbone, the cumulative doses of single chemotherapeutic agents might be reduced. The German Hodgkin Study Group combined the antibody–drug conjugate brentuximab vedotin with a modified eBEACOPP regimen, which is currently being tested against PET-2-guided eBEACOPP in an international phase 3 trial (NCT02661503).[27] Brentuximab vedotin was also combined with AVD (A+AVD) and tested against standard ABVD in a large phase 3 trial.[28,29] Given the modest difference in efficacy between treatment groups, increased toxicity of the A+AVD regimen, and considerable cost of brentuximab vedotin, the debate as to whether A+AVD can be considered as a standard of care is still ongoing. Notably, treatment was not PET-guided and PET-2-positive patients in this trial faced a disappointing outcome, with a 3-year progression-free survival of 69·2% with A+AVD versus 54·7% with ABVD.[29]

Furthermore, the introduction of immunotherapy into first-line treatment might be a promising approach. Several clinical trials are ongoing to address the efficacy and safety of using PD-1 blockade in various combinations with chemotherapy and might offer a new therapeutic approach in first-line advanced-stage Hodgkin lymphoma.

Various limitations of our analysis must be acknowledged. First, the HD18 trial used a conservative definition of PET positivity, including patients with a Deauville score of 3.[11] Today, in line with the excellent outcome of this subgroup in our study, a Deauville score of 3 is widely accepted as negative. In our follow-up trial for advanced-stage Hodgkin lymphoma (NCT02661503), the definition of a positive PET was applied accordingly, and patients with a Deauville score of 3 are now being treated with a shorter regimen of four chemotherapy cycles. Second, the follow-up period in this trial was too short to analyse the full range of late toxicities that might occur decades after treatment for Hodgkin lymphoma. As the trial has ended and no further follow-up beyond 5 years is being documented, we will not be able to address this important question within this trial cohort. Third, analysis of late toxicities was hampered by the small number of patients with available follow-up data. Importantly, the baseline levels of left ventricular ejection fraction and diffusion capacity of the lung in patients with available follow-up data appear to be similar to those of all patients with available baseline data, so the possibility of a relevant selection bias can be excluded from our analysis. However, the results must still be interpreted with caution. Moreover, no qualitative data for important fertility measures, such as sperm and hormone concentrations, were available for our HD18 trial cohort. As these data are of utmost importance, we are assessing them in our follow-up trial (NCT02661503), which examines PET-guided eBEACOPP variants in advanced-stage Hodgkin lymphoma.

Taken together, the reduction from eight to four cycles of eBEACOPP for patients with a negative PET-2 maintains excellent disease control, improves treatment tolerability, and substantially shortens treatment duration, and thus should be considered standard of care for this patient cohort. The change from eight to only four cycles of eBEACOPP represents a benchmark in the treatment of early-responding patients with advanced-stage Hodgkin lymphoma, who now can be potentially cured with a short and safe treatment approach. The efficacy and safety of PET-2-guided treatment with upfront eBEACOPP both contribute to the outstandingly low relapse rates and high overall survival rates observed in this study. The results of the HD18 trial should therefore set the standard for future developments about the risk–benefit ratio in the treatment of newly diagnosed advanced-stage Hodgkin lymphoma.

Contributors

SK, AM, RG, DAE, JMZ, JMa, JMe, MF-B, MS, H-JB, WW, W-DL, TP, MST, FH, MB, UBK, DK, HO, BH, WA, GM, and TV directed clinical activities at participating study centres. HS led the reference pathology. CK, HE, CB, MF, and MD did the central PET review. HG and IB led the statistical analyses of the data. MF directed activities at the German Hodgkin Study Group Trial Coordination Center. AE, VD, and PB led the design of the study protocol. AE is the principal investigator of the study. SK and HG accessed and verified the data. All authors contributed to data interpretation, reviewed the draft, and approved the final version of this report. All authors had full access to all the data in the study, and the corresponding author had final responsibility for the decision to submit for publication.

Declaration of interests

AM reports participation in advisory boards from Roche, Janssen, and Takeda outside the submitted work. RG reports honoraria, a consulting advisory role, research funding, travel, accommodations, and expenses from Celgene, Roche, Merck, Takeda, AstraZeneca, Novartis, Amgen, Bristol Myers Squibb, MSD, Sandoz, Abbvie, Gilead, Daiichi Sankyo, and Janssen outside the submitted work. JMe reports non-financial support from MSD, Bristol Myers Squibb, Takeda, Celgene, and Hexal outside the submitted work. GM reports personal fees from Amgen, Bristol Myers Squibb, Janssen, AstraZeneca, Gilead, and Merck Serono, outside the submitted work. AE reports grants and personal fees from Takeda/Millennium, Bristol Myers Squibb, Hexal, Janssen, AstraZeneca, and Merck outside the submitted work. SK, HG, IB, CK, DAE, JMZ, JMa, MFB, MS, H-JB, WW, W-DL, TP, MST, FH, MB, UBK, DK, HO, BH, WA, TV, HE, CB, HS, MF, VD, MD, and PB declare no competing interests.

Data sharing

The datasets generated and analysed during the current study and single patient data can be made available upon reasonable request. Decisions about data sharing will be made on a case-by-case basis by the corresponding author, considering data protection and other applicable regulations. The trial protocol as well as the statistical analysis plan are provided in appendix 2 for an indefinite period. Proposals can be submitted to the corresponding author.

Acknowledgments

This trial was funded by the Deutsche Krebshilfe (grant numbers 107957 and 110617) and the Swiss State Secretariat for Education, Research and

Innovation (SERI), and supported by Roche Pharma (grant number ML-21683). The Deutsche Krebshilfe provided a grant and reviewed the trial protocol for adherence to good clinical practice. Roche Pharma provided the study drug rituximab for the PET-2-positive patient cohort and financial support.

References

1 Engert A, Haverkamp H, Kobe C, et al. Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial. *Lancet* 2012; **379:** 1791–99.

2 Engert A, Goergen H, Markova J, et al. Reduced-intensity chemotherapy in patients with advanced-stage hodgkin lymphoma: updated results of the open-label, international, randomised phase 3 HD15 trial by the German Hodgkin Study Group. *HemaSphere* 2017; **1:** e5.

3 Eichenauer DA, Thielen I, Haverkamp H, et al. Therapy-related acute myeloid leukemia and myelodysplastic syndromes in patients with Hodgkin lymphoma: a report from the German Hodgkin Study Group. *Blood* 2014; **123:** 1658–64.

4 Josting A, Wiedenmann S, Franklin J, et al. Secondary myeloid leukemia and myelodysplastic syndromes in patients treated for Hodgkin's disease: a report from the German Hodgkin's Lymphoma Study Group. *J Clin Oncol* 2003; **21:** 3440–46.

5 Behringer K, Mueller H, Goergen H, et al. Gonadal function and fertility in survivors after Hodgkin lymphoma treatment within the German Hodgkin Study Group HD13 to HD15 trials. *J Clin Oncol* 2013; **31:** 231–39.

6 Kreissl S, Mueller H, Goergen H, et al. Cancer-related fatigue in patients with and survivors of Hodgkin's lymphoma: a longitudinal study of the German Hodgkin Study Group. *Lancet Oncol* 2016; **17:** 1453–62.

7 Kreissl S, Müller H, Goergen H, et al. Health-related quality of life in patients with hodgkin lymphoma: a longitudinal analysis of the German Hodgkin Study Group. *J Clin Oncol* 2020; **38:** 2839–48.

8 Weihrauch MR, Re D, Bischoff S, et al. Whole-body positron emission tomography using 18F-fluorodeoxyglucose for initial staging of patients with Hodgkin's disease. *Ann Hematol* 2002; **81:** 20–25.

9 Gallamini A, Rigacci L, Merli F, et al. The predictive value of positron emission tomography scanning performed after two courses of standard therapy on treatment outcome in advanced stage Hodgkin's disease. *Haematologica* 2006; **91:** 475–81.

10 Gallamini A, Hutchings M, Rigacci L, et al. Early interim 2-[^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography is prognostically superior to international prognostic score in advanced-stage Hodgkin's lymphoma: a report from a joint Italian-Danish study. *J Clin Oncol* 2007; **25:** 3746–52.

11 Borchmann P, Goergen H, Kobe C, et al. PET-guided treatment in patients with advanced-stage Hodgkin's lymphoma (HD18): final results of an open-label, international, randomised phase 3 trial by the German Hodgkin Study Group. *Lancet* 2017; **390:** 2790–802.

12 Borchmann P, Haverkamp H, Lohri A, et al. Progression-free survival of early interim PET-positive patients with advanced stage Hodgkin's lymphoma treated with $BEACOPP_{escalated}$ alone or in combination with rituximab (HD18): an open-label, international, randomised phase 3 study by the German Hodgkin Study Group. *Lancet Oncol* 2017; **18:** 454–63.

13 Carde P, Karrasch M, Fortpied C, et al. Eight cycles of ABVD versus four cycles of $BEACOPP_{escalated}$ plus four cycles of $BEACOPP_{baseline}$ in stage III to IV, international prognostic score ≥ 3, high-risk Hodgkin lymphoma: first results of the phase III EORTC 20012 intergroup trial. *J Clin Oncol* 2016; **34:** 2028–36.

14 Viviani S, Zinzani PL, Rambaldi A, et al. ABVD versus BEACOPP for Hodgkin's lymphoma when high-dose salvage is planned. *N Engl J Med* 2011; **365:** 203–12.

15 Federico M, Luminari S, Iannitto E, et al. ABVD compared with BEACOPP compared with CEC for the initial treatment of patients with advanced Hodgkin's lymphoma: results from the HD2000 Gruppo Italiano per lo Studio dei Linfomi Trial. *J Clin Oncol* 2009; **27:** 805–11.

16 Mounier N, Brice P, Bologna S, et al. ABVD (8 cycles) versus BEACOPP (4 escalated cycles ≥ 4 baseline): final results in stage III-IV low-risk Hodgkin lymphoma (IPS 0-2) of the LYSA H34 randomized trial. *Ann Oncol* 2014; **25:** 1622–28.

17 Johnson P, Federico M, Kirkwood A, et al. Adapted treatment guided by interim PET-CT scan in advanced Hodgkin's lymphoma. *N Engl J Med* 2016; **374:** 2419–29.

18 von Tresckow B, Kreissl S, Goergen H, et al. Intensive treatment strategies in advanced-stage Hodgkin's lymphoma (HD9 and HD12): analysis of long-term survival in two randomised trials. *Lancet Haematol* 2018; **5:** e462–73.

19 Turner S, Maher EJ, Young T, Young J, Vaughan Hudson G. What are the information priorities for cancer patients involved in treatment decisions? An experienced surrogate study in Hodgkin's disease. *Br J Cancer* 1996; **73:** 222–27.

20 Kreissl S, Goergen H, Müller H, et al. Survivors' perspectives on risks and benefits of Hodgkin lymphoma treatment: results of a survey by the German Hodgkin Study Group. *Leuk Lymphoma* 2019; **60:** 1389–98.

21 van Leeuwen FE, Chorus AM, van den Belt-Dusebout AW, et al. Leukemia risk following Hodgkin's disease: relation to cumulative dose of alkylating agents, treatment with teniposide combinations, number of episodes of chemotherapy, and bone marrow damage. *J Clin Oncol* 1994; **12:** 1063–73.

22 Sandoval C, Pui CH, Bowman LC, et al. Secondary acute myeloid leukemia in children previously treated with alkylating agents, intercalating topoisomerase II inhibitors, and irradiation. *J Clin Oncol* 1993; **11:** 1039–45.

23 Kaldor JM, Day NE, Clarke EA, et al. Leukemia following Hodgkin's disease. *N Engl J Med* 1990; **322:** 7–13.

24 Eichenauer DA, Becker I, Monsef I, et al. Secondary malignant neoplasms, progression-free survival and overall survival in patients treated for Hodgkin lymphoma: a systematic review and meta-analysis of randomized clinical trials. *Haematologica* 2017; **102:** 1748–57.

25 Behringer K, Mueller H, Goergen H, et al. Gonadal function and fertility in survivors after Hodgkin lymphoma treatment within the German Hodgkin Study Group HD13 to HD15 trials. *J Clin Oncol* 2013; **31:** 231–39.

26 van der Kaaij MA, Heutte N, Meijnders P, et al. Premature ovarian failure and fertility in long-term survivors of Hodgkin's lymphoma: a European Organisation for Research and Treatment of Cancer Lymphoma Group and Groupe d'Etude des Lymphomes de l'Adulte Cohort Study. *J Clin Oncol* 2012; **30:** 291–99.

27 Eichenauer DA, Plütschow A, Kreissl S, et al. Incorporation of brentuximab vedotin into first-line treatment of advanced classical Hodgkin's lymphoma: final analysis of a phase 2 randomised trial by the German Hodgkin Study Group. *Lancet Oncol* 2017; **18:** 1680–87.

28 Connors JM, Jurczak W, Straus DJ, et al. Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma. *N Engl J Med* 2018; **378:** 331–44.

29 Straus DJ, Długosz-Danecka M, Alekseev S, et al. Brentuximab vedotin with chemotherapy for stage III/IV classical Hodgkin lymphoma: 3-year update of the ECHELON-1 study. *Blood* 2020; **135:** 735–42.